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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

CANELLA, KAREN A

ART UNIT	PAPER NUMBER
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1642

DATE MAILED: 11/21/2003

20

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/890,496

Applicant(s)

ZYBIN ET AL.

Examiner

Karen A Canella

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☐ Claim(s) 24-41 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☐ Claim(s) 24-41 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 13) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). ____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) ____ 6) ☐ Other: ____

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DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 2, 2003 has been entered.

Claims 39-41 have been added. Claims 24-41 are pending and under consideration. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Claims 34 and 35 are objected to because they depend upon canceled claims.

Claims 24-41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 24 recites "forming a polyacrylamide gel capsule in a tissue of a mammal". It is unclear if forming the capsule entails polymerizing polyacrylamide from monomer, or if forming the capsule refers to the overgrowth in connective tissue after the implantation of a polyacrylamide gel which was polymerized before transplantation. for purpose of examination, both alternatives will be considered.

Claim 24 lacks a pre-amble stating the method objective. Claim 24 is vague and indefinite in the recitation of "wherein the capsule is adapted for cultivating" without an active method step which defines how the adaptation is to be carried out.

Claim 30 recites "subcutaneous injection of a polyacrylamide gel into the mammal". It is unclear if the injection is of polymerized or unpolymerized polyacrylamide gel.

Claim 36 fails to state how the production of the biologically active substance from said cells fulfills the method objective of treating a pathology in a mammal.

Claim 33 lack an active method step for the formulation of the vaccine preparation.

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Claim 36 is vague and indefinite in the recitation of “introducing a polyacrylamide gel into a mammal”. It is unclear if the gel is introduced as polymerized or unpolymerized polyacrylamide.

Claim 40 is vague and indefinite in the recitation of “cultivated”. It is unclear if said cultivation is referring to the growth of said cells before or after transplantation.

Claim 26 is dependent upon claim 25 which is drawn to a mammal which is a human. claim 26 recites “wherein the mammal”. It is unclear if applicant intended claim 26 to be dependent on claim 25, which carried the specific limitation of “human” or claim 24 wherein is broadly drawn to “mammal”.

Claims 29 and 38 recite “newborn rabbits” and “young pigs”. these are relative terms of development, the metes and bounds of which are not defined by the specification or the art. for instance, the abstract of Boes et al, (Journal of Helminthology, 2000, vol. 74, pp. 45-52) defines a young pig as less than 8 months old versus the abstract of Kubota et al (Anatomischer Anzeiger, 1988, Vol. 166, pp. 117-131) which defines a young pig as 2 months old.

Claims 24-30 and 39-41 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

(A) As drawn to new matter

Claim 24 is drawn to a method comprising forming a polyacrylamide gel capsule in a tissue of a mammal wherein the capsule is adapted for cultivating transplanted allogenic or xenogenic cells for a period of time. Claim 25 embodies the method of claim 24 wherein the mammal is a human. Claim 26 embodies the method of claim 25 wherein the mammal suffer from a pathology and the method comprises cultivating in said polyacrylamide gel capsule transplanted allogenic or xenogenic cells that aid in treating the pathology. Claim 27 embodies the method of claim 26 wherein the pathology is diabetes mellitus. Claim 28 embodies the method of claim 26 wherein pancreatic beta cells are cultivated in said gel capsule. Claim 29 specifies that the pancreatic cells of claim 28 are from newborn rabbits or young pigs. Claim 30 embodies the method of claim 24 wherein the polyacrylamide gel capsule is formed by

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subcutaneous injection of a polyacrylamide gel into the mammal. Claims 24-30 carry the specific limitation of a capsule that is "adapted" for cultivating transplanted or allogenic cells for a period of time. It is noted that the specification as filed does not contain this limitation in reference to the capsule. The specification provides support only for the formation of connective tissue around the implanted polyacrylamide gel. However, lacking a specific definition of the metes and bounds of adapted, the claims can be read as relying upon capsules which are physically or chemically modified by means not disclosed in the specification. Therefore, the limitation of "adapted" in reference to the capsule is broader than the originally disclosed connective tissue capsule. One of skill in the art would conclude that applicant was not in possession of the claimed method reliant upon adapted capsules at the time the application was filed.

Claim 39 embodies the method of claim 24 wherein said period of time is up to 100 days. Claim 40 embodies the method of claim 31 wherein said cells are cultivated for a period of up to 100 days. Claim 39 embodies the method of claim 36 wherein said transplanted cells persist for up to 100 days. Neither the specification nor the claims as originally filed provide support for the specific limitation of "up to 100 days". One of skill in the art would conclude that applicant was not in possession of the invention of claims 39-41 at the time of filing.

(B) As drawn to inadequate written description.

Claims 24-30 require the specific embodiment of a capsule "adapted" for the cultivation of transplanted allogenic or xenogenic cells.

The specification teaches the growth of a connective tissue layer around the periphery of injected polyacrylamide gel. The specification does not provide specific teachings as to the physical or chemical characteristics of a polyacrylamide gel that would favor this capsule formation. As stated below, Pavlyk (EP 742,022) teaches that 14 days after the implantation of polyacrylamide hydrogen, the formation of a fibroblastic reaction including the formation of a connective tissue capsule around the implanted gel. thus it is concluded that the formation of this capsule is inherent after injection of polyacrylamide gel into the host. However, when given the broadest reasonable interpretation, and "adapted" capsule reads on a much broader scope than the formation of a connective tissue capsule, such as chemical derivitization of the polyacrylamide, or the inclusion of an additional substance within the polyacrylamide either after

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or before polymerization. Thus the claims are dependent upon a genus of "adapted" capsules. The genus is highly variant because it encompasses species which have numerous structural and functional attributes which would fall within the limitation of "adapted" such as different chemical and physical properties of the polyacrylamide gel, as stated above. The disclosure of a connective tissue capsule does not adequately describe this genus of "adapted" capsules because the genus of adapted capsules is highly variants encompassing members with different structural and functional attributes which differ from the connective tissue capsule. Thus, one can reasonably conclude that applicant was not in possess of the genus of "adapted" capsules at the time the invention was filed. Therefore, applicant was not in possession of the method claims dependent upon the genus of adapted capsules because if a product which is required by a method is not adequately describes, it is logically deduced that said method cannot be adequately described.

Claims 24-33 and 36-41 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the transplantation of exogenous pancreatic islet s cells and tumor cells into a mammal in need of insulin or immune stimulation against antigens from the transplanted tumor cells, wherein the transplanted cells are maintained for an unspecified length of time, does not reasonably provide enablement for wherein the cells are maintained within the mammal for a specified length of time. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specific embodiments of claims 24-30 and 39-41 are recited above.

Claim 31 is drawn to a method of cultivating allogenic or xenogenic cells of a mammal comprising introduction a polyacrylamide gel into a mammal, thereby inducing the formation of a connective tissue capsule around said gel, and thereafter injecting allogenic or xenogenic cells of a mammal into said gel. Claim 32 embodies the method of claim 31 wherein the gel is introduced by subcutaneous injection. Claim 33 embodies the method of claim 31 which comprises formulating a vaccine preparation comprising said cultivated cells. Claim 36 is drawn to a method of treating a pathology in a mammal comprising introducing a polyacrylamide gel into a mammal thereby inducing formation of a connective tissue capsule around said gel, and

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thereafter transplanting allogenic or xenogenic cells of a mammal into said gel, said cells producing a biologically active substance which is released from said capsule. Claim 37 embodies the method of claim 36 wherein said pathology is diabetes mellitus and said transplanted cells are pancreatic beta cells and said biologically active substance is insulin. Claim 38 embodies the method of claim 37 wherein said beta cells are from newborn rabbits or young pigs. the specific embodiments of claims 39-41 are set forth above.

Topalov et al teach a polyacrylamide gel which is polymerized, macerated and sterilized for use as an endoprosthesis for cosmetic and structural replacement of tissue areas and for increasing the turgor of tissues (WO 99/10021). the material taught by Topalov et al appears to have the same chemical and physical properties of the gel described in the partial translation of RU 2127129, the foreign priority document on which the instant application depends. Pavlyk (EP 742,022) teaches that 14 days after the implantation of polyacrylamide hydrogel, the formation of a fibroblastic reaction including the formation of a connective tissue capsule around the implanted gel was noted and that after one month after the injection of the polyacrylamide hydrogel a mature connective tissue capsule was formed surround said gel (page 11, lines 21-36). Chaikof (Annual Review of Biomedical Engineering, May 1999, vol. 1, pp. 103-127) teaches that allogenic and xenogenic pancreatic islet cells have been investigated as potential sources for donor transplantation. Chaikof teaches that the microenvironment at the site of the transplantation, including the availability of oxygen and nutrients influence the performance of transplanted cells (page 104, lines 1-4 under the heading "Cell Sourcing", and page 106, lines 1-4, under the heading "Optimizing the Viability and Function of the Transplanted Cell"). Chaikof specifically teaches that the development of a fibrotic tissue reaction in the region of the implant further limits the amount of oxygen and nutrients which are available to the transplanted cells by increasing the distance between the blood vessels and the implant and establishing a layer of oxygen consuming fibroblasts (page 106, lines 12-15 under the heading "Optimizing the Viability and function of the Transplanted Cell"). The instant claims 31-33 and 36-38 require that a connective tissue capsule is formed around the gel. One of skill in the art would reasonable conclude that the formation of said connective tissue capsule would further limit the access of oxygen and nutrients to the transplanted cells. The instant specification does not teach how to maintain cells for up to 100 days in conditions inside a capsule surrounded by connective

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tissue. It would be expected that the cells would have decreased metabolic function and decreased viability under hypoxic and starvation conditions. The specification does not address these limitations or provide specific examples which overcome these limitations.

Chaikof further teaches that in the situation of encapsulated islet cells, it is likely that xenogenesis antigens, or non-antilogous antigens are released from the capsule either by being shed from the encapsulated cells or from an occasional broken capsule. These antigens will be processed by antigen presenting cells within the host leading to the upregulation of the immune response in the host against said antigens. (page 107, line 13 of the second paragraph to page 108, line 10). Chaikof teaches that once the immune response is primed against the transplanted cells, the design constraints for achieving an effective barrier are much more severe. (page 108, lines 17-18). Chaikof concludes that the requirement for an immunoisolation barrier for transplanted cells would include the preventing the release of shed antigens (page 108, lines 13-16). Wang et al (Nature Biotechnology, 1997, vol. 15, pp. 358-362) teach that islet cells encapsulated in sodium alginate teach that the eventual failure of encapsulated islet cells did not result from capsule rupture or infiltration of immune cells. Wang et al pointed out that some failed capsules retrieved from implanted mammals were free of fibrosis and attributes the death of the encapsulated islet cells to nutrient deficiency or soluble immune factors (page 361, second column, lines 1-8). the specification does not address these technical difficulties or provide guidance in overcoming the problem of shed antigens inducing soluble immune factors, and hypoxia and nutrient deficiency.

Given the lack of teachings in the specification regarding the issues above and the unreliable state of the art regarding the transplantation and immunoisolation of said transplanted cells, one of skill in the art would be subject to undue experimentation in order to carry out the claimed method wherein the transplanted cells were viable for a specific period of time or for up to 100 days.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

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(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 24 is rejected under 35 U.S.C. 102(b) as being anticipated by Lamberti (US 5,827,707). Claim 24 is drawn to a method comprising forming a polyacrylamide gel capsule in a tissue of a mammal wherein the capsule is adapted for cultivating transplanted allogenic or xenogenic cells for a period of time.

Lamberti discloses a method of treating a diabetic athymic mouse comprising implanting porcine pancreatic islets into a polymer (column 8, line 65 to column 9, line 20). It is noted that the athymic mouse would not be able to amount a cell-mediated immune response against a foreign antigen. Lamberti discloses that polyacrylamide is used in the making of the polymer encapsulated cells (column 3, line 63 to column 4, line 15). Because the specification does not provide a definition of the metes and bounds of an "adapted" capsule which would exclude microencapsulation as an adaptation means to cultivate xenogenic or allogenic cells in a host.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

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Claims 24-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lamberti (US 5,827,707) in view of Chaikof (Annual Review of Biomedical Engineering, 1999, vol. 1, pp. 103-107) and Sefton and Stevenson (Advances in Polymer Science, 1993, vol. 107, pp. 143-197). The specific embodiments of the claims are set forth above.

Lamberti teaches a method of treating a diabetic athymic mouse comprising implanting porcine pancreatic islets into a polymer (column 8, line 65 to column 9, line 20). It is noted that the athymic mouse would not be able to mount a cell-mediated immune response against a foreign antigen. It is also noted that the metes and bounds of a "young" pig have not been defined, therefore the disclosure of porcine islets fulfills the specific limitation of claim 29. Lamberti teaches that polyacrylamide is used in the making of the polymer encapsulated cells (column 3, line 63 to column 4, line 15) in the . Because the specification does not provide a definition of the metes and bounds of an "adapted" capsule which would exclude microencapsulation as an adaptation means to cultivate xenogenic or allogenic cells in a host. Lamberti suggest that the use of microencapsulated islets can be used for the treatment of diabetes mellitus in humans (column 1, lines 9-14). Lamberti does not specifically teach a method of treating a human suffering from diabetes mellitus.

Chaikof teaches that successful xenograft cell transplantation is expected to require at a minimum, use of an ultra filtration membrane to reduce soluble antigen release, whereas a micro filtration membrane may suffice for allograft cell transplants (page 113, lines 11-14 under the heading "Materials and Membrane-Forming Processes"). Chaikof teaches that the phase inversion technique can control the porosity of the membrane obtained around the encapsulated cells (page 113, lines 8-11, last paragraph). Chaikof refers to the experiments of Sefton and Stevenson (Advances in Polymer Science, 1993, vol. 107, pp. 143-197) who teach the microencapsulation of a variety of cells in polyacrylates by means of phase inversion precipitation including polymers containing dimethylaminoethyl methacrylate which would result in a polyacrylamide (page 182 to 184, under section 4.3, "Encapsulation of Nucleated Cells").

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to encapsulate porcine islets cells or allogenic islet cells in polyacrylamide


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using the phase inversion method and implant said cells into a human for the treatment of diabetes.

One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Chaikof on the necessity for having a small membrane porosity to limit the amount of shed antigen in xenogenic transplanted cells and the teachings of Chaikof on the ability to control membrane porosity in the microencapsulation technique by the use of phase inversion. One of skill in the art would be motivated to control the porosity of the membrane to limit the shedding of non-self antigens from the xenogenic cells, and to not unduly limit the flow of oxygen and nutrients in the case of allogenic cells because these are factor which limit the viability of the transplanted cells in vivo.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.


Karen A. Canella, Ph.D.

Patent Examiner, Group 1642

11/17-03